CHAPTER 17

Depression

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Every year 20.9 million Americans suffer from a depressive illness. Among primary care patients, the incidence of depression may be as high as 8.6%. Depression is a major cause of suicide and disability, and complicates other chronic medical conditions like CAD and diabetes. Because safe, effective, evidence-based treatments are widely available, it is important to identify patients with depressive illnesses. Note that TCAs, once widely used, are rarely indicated as first-line treatment due to severe toxicity in overdose. Classification of depressive disorders is based on the DSM-IV-TR. This chapter reviews important mood disorders seen in primary care.

DEPRESSIVE DISORDERS

There are five depressive illnesses most relevant to primary care: major depression, minor depression, postpartum depression, dysthymia, and seasonal affective disorder (SAD). Each disorder is a syndrome defined by a certain number of depression symptoms occurring with a specific duration or timing (Table 17-1). For each disorder symptoms are present most of the day, nearly every day, and lead to significant distress or impairment in social, occupational, or other areas of functioning.

MAJOR DEPRESSIVE EPISODE

Symptoms

- Depressed mood (children: may be irritable mood) +++++
- Anhedonia, diminished interest or pleasure in all or almost all activities +++++
- Weight loss (more common) or weight gain (change of more than 5% body weight within 1 month) or change in appetite (decrease more common than increase) (children: failure to achieve expected weight) +++
- Insomnia (most common manifestation), early morning awakening or hypersomnia ++++
- Fatigue, loss of energy or sense of being “slowed down” ++++
- Restlessness ++++
- Feelings of worthlessness or excessive or inappropriate guilt ++++

Table 17-1. Depressive Disorders

SYNDROME	DSM-IV CRITERIA	DURATION, TIMING
Major depressive episode	At least five depressive episode symptoms including depressed mood or anhedonia	Symptom duration at least 2 weeks
Minor depressive episode	Two to four depressive episode symptoms including depressed mood or anhedonia	Symptom duration at least 2 weeks
Postpartum depression	At least five depressive episode symptoms including depressed mood or anhedonia	Symptom duration at least 2 weeks, within four weeks of delivery
Dysthymia	Three or four major depressive episode symptoms including depressed mood; no history of major depressive episode	Symptom duration at least 2 years, no more than 2 months free of symptoms (children, at least 1 year)
Seasonal affective disorder	Depressive episodes with characteristic seasonal pattern	Two episodes with same seasonal timing within last 2 consecutive years

American Psychiatric Association *Diagnostic and statistical manual of mental disorders, IV-R*, 2000, The Association.

- Diminished ability to think, concentrate, or make decisions ++++
- Recurrent thoughts of death, suicidal ideation, or recent suicide attempt +++

Signs

- Flattened affect
- Tearfulness
- Poor eye contact
- Observable psychomotor agitation or retardation ++++

Workup

The clinical interview is used to make a diagnosis of major depression, minor depression, postpartum depression, or dysthymia. Rule out the following before making a diagnosis of major depression, minor depression, dysthymia, or SAD:

- Other psychiatric illnesses, including bipolar disorder (there has never been a manic episode), schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, and psychotic disorder

- General medical conditions solely responsible for the symptoms (e.g., viral illnesses, hypothyroidism, anemia, Cushing's disease, diabetes mellitus, malignancy, CAD, CHF, and autoimmune disorders)
- Side effects of medications (e.g., glucocorticoids, antihypertensives such as beta-blockers or reserpine), alcohol, or withdrawal from drugs of abuse (alcohol, cocaine, or amphetamine)
- Bereavement

MINOR DEPRESSIVE EPISODE

Symptoms

- Depressed mood (children: may be irritable mood) ++++
- Anhedonia, diminished interest or pleasure in all or almost all activities ++++
- Weight loss or weight gain (change of more than 5% body weight within 1 month) or change in appetite (children: failure to achieve expected weight) ++
- Insomnia, early morning awakening, or hypersomnia +++
- Fatigue, loss of energy or sense of being "slowed down" ++++
- Restlessness ++
- Feelings of worthlessness or excessive or inappropriate guilt ++++
- Diminished ability to think, concentrate, or make decisions ++++
- Recurrent thoughts of death, suicidal ideation, or recent suicide attempt ++

Signs

- Flattened affect
- Tearfulness
- Poor eye contact
- Observable psychomotor agitation or retardation ++

Work up

The clinical interview is used to make a diagnosis of major depression, minor depression, postpartum depression, or dysthymia. Rule out the following before making a diagnosis of major depression, minor depression, dysthymia, or SAD:

- Other psychiatric illnesses, including bipolar disorder (there has never been a manic episode), schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, and psychotic disorder
- General medical conditions solely responsible for the symptoms (e.g., viral illnesses, hypothyroidism, anemia, Cushing's disease, diabetes mellitus, malignancy, CAD, CHF, and autoimmune disorders)
- Side effects of medications (e.g., glucocorticoids, antihypertensives such as beta-blockers or reserpine), alcohol, or withdrawal from drugs of abuse (alcohol, cocaine, or amphetamine)
- Bereavement

Special Considerations

Evidence suggests that patients may benefit from antidepressant treatment even if full major depressive episode criteria are not met. There is inadequate evidence to guide therapeutic decision making. Decisions to initiate treatment must involve weighing the degree of functional impairment and duration of minor depression symptoms against the cost and potential side effects associated with the selected treatment.

Medications: Evidence for the efficacy of medication is equivocal. Some studies have demonstrated SSRIs and MAOIs to be effective, whereas others indicated outcomes that were comparable to or worse than placebo. Note potential for drug interactions with MAOIs. SSRIs may improve functional outcomes independent of their effect on minor depression symptoms.

Psychotherapy: Evidence for the efficacy of psychotherapy is also equivocal. Interpersonal psychotherapy and CBT may be effective.

Other interventions: Nonspecific treatments such as empathy from health care clinicians and social involvement may improve symptoms. Large muscle resistance exercise training was effective in one small study.

Authorities in the United States advise caution when prescribing any antidepressant to patients of all age ranges because of the increased risk of suicide (see the following text).

POSTPARTUM DEPRESSION

Symptoms

- Symptoms of major depressive episode
- Difficulty sleeping, when present, occurs even when the baby is sleeping
- "Baby blues" (sadness, anxiety, irritability, confusion) occurs in the majority of mothers by postpartum day 4 and resolves within 10 days.
- Postpartum psychosis (extreme thought disorganization, bizarre behavior, hallucinations) occurs within 2 weeks of delivery; this is a psychiatric emergency due to risk of suicide and infanticide.

Signs

- Flattened affect
- Tearfulness
- Poor eye contact
- Observable psychomotor agitation or retardation

Workup

The clinical interview is used to make a diagnosis of major depression, minor depression, postpartum depression, or dysthymia.

Rule out the following before making a diagnosis of major depression, minor depression, dysthymia, or SAD:

- Other psychiatric illnesses, including bipolar disorder (there has never been a manic episode), schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, and psychotic disorder
- General medical conditions solely responsible for the symptoms (e.g., viral illnesses, hypothyroidism, anemia, Cushing's disease, diabetes mellitus, malignancy, CAD, CHF, and autoimmune disorders)
- Side effects of medications (e.g., glucocorticoids, antihypertensives such as beta-blockers or reserpine), alcohol, or withdrawal from drugs of abuse (alcohol, cocaine, or amphetamine)
- Bereavement

Special Considerations

The general treatment recommendations for a major depressive episode apply, except as noted following.

Medication: SSRI treatment is recommended for all patients. Start dosing at one half the usual dose because postpartum patients may be more susceptible to side effects. Increase the dose in increments of the starting dose.

Breastfeeding and medications: Because all antidepressants are excreted in breast milk, use the lowest effective doses. Sertraline (Zoloft) and paroxetine (Paxil) are often used due to case series data indicating that infants breastfed by mothers taking these medications suffered no significant physiologic adverse effects. Children breastfed by mothers taking SSRIs have not exhibited significant developmental delays or neurologic sequelae.

DYSTHYMIA

Symptoms

- Symptoms of major depressive episode
- Feelings of hopelessness
- Low self-esteem

Signs

- Flattened affect
- Tearfulness
- Poor eye contact
- Observable psychomotor agitation or retardation

Workup

The clinical interview is used to make a diagnosis of major depression, minor depression, postpartum depression, or dysthymia. Rule out the following before making a diagnosis of major depression, minor depression, dysthymia, or SAD:

- Other psychiatric illnesses, including bipolar disorder (there has never been a manic episode), schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, psychotic disorder
- General medical conditions solely responsible for the symptoms (e.g., viral illnesses, hypothyroidism, anemia, Cushing's disease, diabetes mellitus, malignancy, CAD, CHF, and autoimmune disorders)
- Side effects of medications (e.g., glucocorticoids, antihypertensives such as beta-blockers or reserpine), alcohol, or withdrawal from drugs of abuse (alcohol, cocaine, or amphetamine)
- Bereavement

Special Considerations

Medications: SSRIs, TCAs, and MAOIs all have demonstrated efficacy in improving dysthymia symptoms and are considered equally effective. TCAs are highly toxic in overdose and MAOIs have significant drug interactions and therefore are generally not used as front-line agents. Studies indicate pharmacotherapy may be more effective than psychotherapy. The balance between medication side effects and symptom relief may be even more important than for other forms of depression given that dysthymia is chronic and less severe. Therefore, SSRIs are considered to be first-line treatment for dysthymia because TCAs and MAOIs are more likely to cause side effects and adverse events.

Psychotherapy: Psychotherapy has not been proven effective in reducing dysthymia symptoms, whether alone or in combination with medications. Psychotherapy may improve functional capabilities when combined with SSRIs, TCAs, or MAOIs.

Comments and Treatment Considerations for All Depressive Disorders

Assessment for suicidal ideation is critical. For each patient who has depressive symptoms, determine the following:

- Presence of passive death wish: "Have you been thinking that it would be easier if you were dead, or that life is not worth living?"
- Presence of active suicidality: "Have you been thinking about ending your life?"
- Presence of plans if suicidal ideation is present: "Do you have a plan for ending your life?"
- State of readiness to commit suicide: Possession of weapons or deadly items, possession of items included in the suicide plan, a set timeline for carrying out the plan, or triggers for implementing the plan
- Presence of furtherance of plan: Has the patient taken active steps to obtain items (e.g., weapons) or arrange conditions (e.g., gave away a pet) needed to complete the suicide plan?

A primary care clinician can treat the majority of people with depression. In emergencies or severe cases, specialist evaluation is indicated.

Indications for emergent psychiatrist evaluation or hospitalization: Plans to commit suicide characterized by readiness and/or furtherance, plans to harm others (including the patient's children) (for postpartum depression: postpartum psychosis or inability to care for the infant), life-threatening behaviors (e.g., refusal to eat).

Indications for psychiatric referral: Severe functional impairment, suspicion of mania/bipolar symptoms, psychotic symptoms, suicidal ideation with or without a specific plan, comorbid eating disorder, alcohol abuse or other substance abuse, and treatment-resistant depression.

Treatment phases and monitoring: There are three consecutive treatment phases: acute, continuation, and maintenance.

ACUTE PHASE

- Initial presentation to end of depression: Adjust treatment modalities as needed.
- Failure to treat until complete depression remission results in poorer functional outcomes and increased risk of depression relapses.

Continuation phase: Designed to prevent depression relapse, and involves continued treatment for an additional 4 to 5 months.

Maintenance phase: The maintenance phase involves ongoing treatment with antidepressant medication and/or psychotherapy to prevent depression recurrence. Maintenance treatment is according to patient preference or for patients who have had three or more major depressive episodes, severe depressive episodes, dysthymic symptoms after major depression remission, or comorbid psychiatric illnesses.

Treatment monitoring: Patients should initially be seen every 2 weeks until the depressive symptoms remit. Factors indicating the need for more frequent follow-up include suicidal ideation, more severe symptoms, inadequate social support, and comorbid medical problems.

Selecting treatment modalities: The most commonly applied therapies for depressive episodes are antidepressant medication and psychotherapy, which have comparable efficacy for mild to moderate depressive episodes. Both medication and psychotherapy significantly improve depression severity by 12 months. Although medications lead to more rapid remission, psychotherapy can treat and prevent depressive episodes by helping patients build coping strategies and redirect negative thought processes.

Patients undergoing psychotherapy must be motivated to experience significant reductions in depressive symptoms. The best treatment outcomes are achieved with a combination of medication and psychotherapy. For mild to moderate depression, patients should be encouraged to select from these treatment modalities based on their personal preferences. For patients with moderate to severe

depression, medication should be used in nearly all cases, accompanied by psychotherapy for patients who are motivated and/or have prominent interpersonal or psychosocial problems. Consider adding another form of treatment when depression symptoms do not fully respond to the initially selected treatment modalities. Electroconvulsive therapy (ECT) should be considered for patients with severe depression, life-threatening or treatment-resistant symptoms, psychosis, need for rapid improvement, or previous success with the modality.

Initial medication selection: The SSRIs, the serotonin norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine, the dopamine norepinephrine reuptake inhibitor (DNRI) bupropion, the TCAs, the MAOIs, and the tetracyclic antidepressant mirtazapine have been shown equally effective in promoting remission of depression; all proved more effective than placebo. SSRIs are considered first-line treatment. SSRIs are better tolerated and are associated with less treatment discontinuation than TCAs, which have high risk of morbidity and mortality in overdose. MAOIs have significant side effects, and important (and potentially life threatening) drug and food-drug interactions. Many SSRIs are available as generic formulations. When selecting a medication, incorporate patients' unique needs by considering the following factors: side effect profiles, adverse effect profiles, the medications' relative safety in overdose, the patient's history of success with particular medications, family member's history of success with particular medications, medication cost, dosing frequency, and the patient's preferences. Table 17-2 lists commonly used antidepressants.

Managing medications: Start with half the usual recommended initial dose for older adult patients or patients who have comorbid panic or anxiety symptoms. For patients recently started on a new medication or had a medication dose increase, arrange frequent follow-up (every 2 weeks) to assess for side effects, adherence, emergent suicidality, development of mania, symptom improvement, and functional improvement. Allow 6 to 8 weeks for the patient to experience the full effects of any given dose.

Inadequate medication response: If there is no change or only partial remission of symptoms, first assess adherence to the medication regimen and inquire about medication side effects (see earlier). If adherence is adequate and there are no significant side effects, consider increasing the medication towards its maximum daily dose or to the maximum dose the patient will tolerate. If there is no change in symptoms consider switching to another antidepressant from the same class. If two medications from the same class were both ineffective, consider switching to a medication from a different class. Bupropion or venlafaxine is frequently used when two or more SSRIs have been ineffective. If the symptoms are partly improved and the medication dose is maximal (either at the dose listed in Table 17-2 or limited by side effects), consider augmenting with another medication from a different class. Evidence strongly supports the use of lithium for antidepressant augmentation. Bupropion also has proven

Table 17-2. Commonly Used Antidepressant Medication Adult Doses and Side Effects

MEDICATION	INITIAL DOSE (mg/day)	MAXIMUM DOSE (mg/day)	COMMON SIDE EFFECTS
Selective Serotonin Reuptake Inhibitors (SSRIs)			
Citalopram (Celexa)	20	60	Dry mouth, increased sweating, nausea, somnolence, insomnia, tremor, diarrhea, delayed ejaculation, anorgasmia
Escitalopram (Lexapro)	10	20	Dry mouth, nausea, somnolence, insomnia, diarrhea, delayed ejaculation, anorgasmia
Fluoxetine (Prozac)	20	80	Headache, asthenia, nausea, diarrhea, anorexia, dry mouth, dyspepsia, insomnia, nervousness, anxiety, somnolence, dizziness, tremor, increased sweating, delayed ejaculation, anorgasmia
Paroxetine (Paxil)	Regular: 20 Controlled release: 25	Regular: 50 Controlled release: 65	Headache, asthenia, increased sweating, nausea, dry mouth, constipation, diarrhea, decreased appetite, somnolence, dizziness, insomnia, tremor, delayed ejaculation, anorgasmia, erectile dysfunction
Sertraline (Zoloft)	50	200	Delayed ejaculation, anorgasmia, dry mouth, increased sweating, somnolence, dizziness, headache, tremor, anorexia, constipation, diarrhea, dyspepsia, nausea, fatigue, insomnia, decreased libido

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)				
Duloxetine (Cymbalta)	40 (divided bid)	60 (may be given daily or divided bid)		Nausea, dry mouth, constipation, diarrhea, vomiting, anorexia, fatigue, dizziness, somnolence, increased sweating, insomnia, anorgasmia
Venlafaxine (Effexor)	Regular: 75 (divided bid-tid) Extended release: 75	Regular: 375 (divided tid) Extended release: 375		Headache, asthenia, infection, increased sweating, nausea, constipation, anorexia, diarrhea, vomiting, somnolence, dry mouth, dizziness, insomnia, nervousness, anxiety, blurred vision, delayed ejaculation/orgasm, erectile dysfunction
Other				
Bupropion (Wellbutrin)	Sustained release: 150 Extended release: 150	Sustained release: 400 (divided bid) Extended release: 450		Headache, infection, dry mouth, nausea, constipation, insomnia, dizziness, tremor, increased sweating, tinnitus, agitation, anxiety, abdominal pain, palpitations, diarrhea, myalgia, pharyngitis
Mirtazapine (Remeron)	15	45		Drowsiness, increased appetite, weight gain, dizziness, anxiety, confusion, dry mouth, constipation, upset stomach, vomiting

efficacy in augmenting partially effective SSRI regimens. Other potential options for antidepressant augmentation include liothyronine (T_3, Cytomel) and psychostimulants such as methylphenidate.

Handling medication side effects: Side effects are the most common reason for antidepressant discontinuation (see Table 17-2). Many patients initially treated with an SSRI will have to switch to another agent due to side effects. If a patient develops mania after starting an antidepressant medication, he or she may have bipolar disorder; the medication should be tapered and the patient should be referred to a psychiatrist immediately for evaluation. Counsel all patients taking antidepressant medications about the side effects they might experience, including suicidality (see following text). Let them know which side effects should be reported immediately. Medication side effects often resolve within 1 to 2 weeks, so watchful waiting is acceptable if the patient is able to tolerate them and they do not pose a medical risk. If the side effects are intolerable, switch to another medication.

Sexual side effects: Sexual side effects are very common and frequently lead to discontinuation of SSRIs and SNRIs. Ask patients directly whether they are experiencing these symptoms. Decreasing the medication dose or instituting drug holidays (e.g., skipping doses on days of sexual activity) can ameliorate sexual side effects, but these strategies should be used with caution because they could lead to poor regimen adherence. Another option is to add a medication that can counteract the sexual side effects such as buspirone or bupropion. Medications such as sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) can also be effective in treating SSRI-induced sexual dysfunction in men. Finally, the offending medication could be discontinued in favor of another medication that is less likely to cause significant sexual side effects (e.g., a medication from the same class, bupropion, or mirtazapine).

Antidepressants and risk of suicide: The early phases of antidepressant treatment are often activating and may lead to increased agitation and energy relative to the depressed baseline state. Because patients frequently continue to experience a sense of hopelessness during this period, they may be at increased risk for suicidal ideation and suicide attempts. There is not sufficient evidence to rule out the possibility of increased suicide risk. Decisions to institute antidepressant medications should always involve a careful balance of the known benefits and risks. Authorities in the United Kingdom have advised against using the following antidepressants among children: paroxetine, citalopram, venlafaxine, escitalopram, and mirtazapine. Authorities in the United States advise caution when prescribing any antidepressant to patients of all age ranges. During the initial months of treatment with an antidepressant medication, patients must have frequent follow-up visits (e.g., every 2 weeks). Counsel all patients starting antidepressants about the risk of agitation and suicidality, and advise them to seek medical advice immediately if they experience these symptoms. Caregivers and family members must be educated to monitor the patient and immediately seek medical advice if the patient exhibits worsened symptoms, suicidality, or unusual behaviors.

Discontinuation of medications: After the continuation phase of antidepressant treatment, if maintenance treatment is not selected, antidepressant medications should be tapered over at least 1 month to reduce the risk of depression recurrence. Even when they are discontinued prior to depression remission, most antidepressant medications should be tapered to prevent withdrawal symptoms. Withdrawal symptoms may include dizziness, nausea, paresthesia, headache, and vertigo. Because fluoxetine and its metabolites have longer half-lives, this medication may not exhibit as significant withdrawal symptoms when abruptly discontinued.

Selecting psychotherapies: Systematic reviews indicate that both structured and nonstructured psychotherapies achieve better outcomes than placebo or usual care. The best-studied structured psychotherapeutic modalities are CBT and interpersonal therapy; these have comparable efficacy.

Use of ECT: Given the availability of effective antidepressant medications and psychotherapies, use of ECT is limited to patients who cannot take medications, have treatment-resistant depression, have severe or psychotic symptoms, have catatonia, or have life-threatening symptoms such as suicidality or refusal to eat. Compared to medications, ECT is proven to provide more rapid short-term improvement in patients with moderate to severe depression symptoms. ECT may lead to cognitive impairment but this is usually limited to short-term memory loss during treatment.

SEASONAL AFFECTIVE DISORDER

SAD is characterized by the onset and remission of depressive symptoms during specific seasons. SAD is categorized by DSM-IV as a subtype of major depression. Depressive episodes associated with recurrent major depression, or bipolar I or bipolar II disorders (see later discussion about bipolar disorder) can have a seasonal timing. Typically the onset is in the fall and remission is in the spring, but in 10% of cases depression onset may occur in the summer. SAD is more common among women, those living farther from the equator (for winter depression), and those who are 20 to 30 years old. It is important to recognize SAD because the treatment differs from other forms of depression.

Recurrent seasonal onset and seasonal remission of major depression symptoms for at least 2 years in a row defines SAD. Symptoms are generally characteristic of major depressive episodes (see previous section). Winter and summer depression may have a different constellation of symptoms.

WINTER DEPRESSIVE EPISODES

Symptoms

- Oversleeping
- Daytime fatigue

- Craving carbohydrates (sweets, starches)
- Weight gain
- Irritability
- Heavy feeling in arms and legs
- Symptoms associated with more overcast weather, darkened interior lighting, or working in an office building with few windows

Signs

- Regular temporal relationship between specific time of year and onset of major depressive episodes in recurrent major depressive disorder, bipolar I or bipolar II disorders
- Full remission of depression symptoms (orchange to mania or hypomania) also occurs at predictable times of year.
- Two major depressive episodes in the last 2 years with onset and resolution in characteristic seasons
- No nonseasonal major depressive episodes in the last 2 years
- Lifetime pattern whereby most major depressive episodes were seasonal
- Typically onset in fall and remission in spring

Workup

- Exclude seasonal-related psychosocial factors (e.g., holiday-related stress, losing seasonal work with changing weather).
- Exclude medical conditions solely responsible for the symptoms (e.g., hypothyroidism, hypoglycemia, infectious mononucleosis, other viral illnesses).

Comments and Treatment Considerations

Patients should be encouraged to guide the treatment selection based on their preferences. Patients with mild symptoms may improve with simple adjustments to increase light exposure (e.g., getting more exposure to daylight during winter months, lighting interior spaces with sunlight or bright lights). However, it is light therapy and antidepressant medications that have been proven effective in treating SAD. Fluoxetine and light therapy appear to be equally effective, although patients taking light therapy typically improve more rapidly (within 1 week) and experience fewer side effects. Medication may be more practical than light therapy for certain patients. Patients who have more severe symptoms or other depressive episodes with a nonseasonal pattern may require combination therapy with light and medications.

Light therapy: This modality has been shown to reverse winter depressive episode symptoms in 50% to 80% of patients. The treatment requires special lighting equipment capable of simulating full-spectrum bright light. Symptoms typically resolve within 2 to 4 days of starting treatment, but several weeks may be required.

Implementing light therapy: Effective light boxes deliver light at an intensity of 10,000 lux. Light therapy should occur in the early morning, and be set at eye level or above (and tilted down toward the patient's head). Therapy starts with 10- to 15-minute sessions and is titrated weekly in 15-minute increments up to 30 to 90 minutes per day.

Light therapy must be continued throughout the fall or winter seasons to prevent recurrence of symptoms. It is discontinued in the spring.

Side effects of light therapy: Side effects are relatively common but typically resolve within the first 5 days and may include headache, eyestrain, visual blurring, residual visual glare, insomnia, nausea, vomiting, hypomania, agitation, sedation, dizziness, and irritability.

If light therapy is inadequate or not tolerated: Medication and/or psychotherapy may be initiated (see later).

Medication: Fluoxetine, sertraline, and hypericum extract (e.g., St. John's wort dosed at 900 mg/day) all have demonstrated efficacy in achieving remission of SAD.

Comorbid bipolar I or bipolar II disorder or summer/spring hypomania: Patients must be on a mood stabilizer before SAD treatment is initiated because both light therapy and medications can induce mania or hypomania.

Relapse prevention: Initiate light therapy, bupropion, or CBT prior to the expected onset of SAD symptoms. Citalopram administered immediately following light therapy–mediated remission has been shown to prevent relapse.

SUMMER DEPRESSIVE EPISODES

- Insomnia
- Decreased appetite
- Weight loss
- Agitation or anxiety

Signs

- Regular temporal relationship between specific time of year and onset of major depressive episodes in recurrent major depressive disorder, bipolar I or bipolar II disorders
- Full remission of depression symptoms (or change to mania or hypomania) also occurs at predictable times of year.
- Two major depressive episodes in the last 2 years with onset and resolution in characteristic seasons
- No nonseasonal major depressive episodes in the last 2 years
- Lifetime pattern whereby most major depressive episodes were seasonal

Workup

- Exclude seasonal-related psychosocial factors (e.g., holiday-related stress, losing seasonal work with changing weather).
- Exclude medical conditions solely responsible for the symptoms (e.g., hypothyroidism, hypoglycemia, infectious mononucleosis, other viral illnesses).

Comments and Treatment Considerations

There is little therapeutic research regarding summer depressive episodes to guide treatment decisions. Medication is typically

prescribed for moderate to severe symptoms (see medication information in "Winter Depressive Episodes").

As noted for the depressive disorders in the previous section, all patients must be assessed for suicidal ideation. Treatment is needed when the symptoms lead to significant distress or impairment in social, occupational, or other areas of functioning. Treatment is different for winter and summer depression episodes.

BIPOLAR DISORDERS AND CYCLOTHYMIA

Bipolar disorder is a syndrome characterized by recurrent episodes of mania/hypomania and depression. Many patients presenting to primary care physicians with depressive symptoms actually have a bipolar disorder. It is crucial for primary care physicians to differentiate between unipolar major depression and bipolar disorder because antidepressant medications can trigger manic/hypomanic episodes in people with bipolar disorder. Bipolar disorder can be difficult to diagnose for two important reasons. First, patients with bipolar disorder frequently present with depressive symptoms as their index episode. Second, many patients do not recognize or report past manic/hypomanic episodes.

Patients with bipolar disorder should be referred to psychiatrists for management. Patients with bipolar disorder are at a higher risk for suicide and tend to exhibit profound impairments in social and occupational functioning. Management of manic and depressive symptoms often requires multiple medications.

Primary care physicians should be aware of the presenting symptoms and management of bipolar illnesses. There are three subtypes of bipolar illness most relevant to primary care: bipolar I, bipolar II, and cyclothymia. Each disorder is defined by a specified pattern of depressive symptoms, full major depressive episodes, manic episodes, or hypomanic episodes occurring during a specific period of time (Table 17-3). For each disorder, symptoms are present most of the day, nearly every day, and lead to significant distress, impairment, or changes in social, occupational, or other areas of functioning.

MANIC EPISODE

This is a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting at least 1 week (a shorter duration is allowed if hospitalization is required). The disturbance is severe, causing at least one of the following: marked impairment in occupational, social, or interpersonal relationship functioning; requirement for hospitalization to prevent harm to self or others; and psychotic features. At least three of the following persistent and significant symptoms are required (four if the mood is only irritable):

Table 17-3. Manic/Hypomanic Disorders

SYNDROME	MANIC SYMPTOM CRITERIA	DEPRESSIVE SYMPTOM CRITERIA	DURATION, TIMING
Bipolar I	One or more manic episodes or mixed depressive or manic episodes	Major depressive episodes	Chronic or episodic Manic episode ≥1 week Major depressive episode ≥2 weeks
Bipolar II	One or more hypomanic episodes; no history of manic or mixed episodes	Major depressive episodes	Chronic or episodic Hypomanic episode ≥4 days Major depressive episode ≥2 weeks
Cyclothymia	Periods of hypomanic symptoms	Periods of depressive symptoms not meeting criteria for major depressive episodes	Chronic or persistent Symptom duration at least 2 years, no more than 2 months free of symptoms (children: at least 1 year)

Adapted from the American Psychiatric Association*: Practice guideline for the treatment of patients with bipolar disorder,* 2nd ed. Available at www.psych.org/psych_pract/treatg/pg/bipolar_revisebook_index.cfm (accessed Oct 17, 2006).

Symptoms*

- Inflated self-esteem ++++
- Decreased need for sleep ++++
- Uncharacteristically talkative or internal pressure to keep talking ++++
- Subjective experience of racing thoughts ++++
- Easy distractibility ++++
- Psychomotor agitation or increase in goal-directed occupational, educational, social, or sexual activity ++++
- Excessive involvement in pleasurable activities with high potential for painful consequences (e.g., shopping sprees, sexual indiscretions) +++

*NOTE: Symptoms must not meet criteria for a mixed episode (see later).

Signs

- Grandiosity
- Pressured speech
- Flight of ideas
- Easy distractibility
- Psychomotor agitation or retardation

Comments and Treatment Considerations

Selecting an initial medication: Bipolar disorder with a current manic episode should always be treated with one or more mood stabilizers. Mild to moderate cases are typically treated with monotherapy using lithium, divalproex, or a second-generation antipsychotic (e.g., olanzapine or risperidone). Any manic episode with psychotic features should be treated with an antipsychotic. Although the three medication types have no significant differences in remission rates (except in bipolar II, mixed episodes, and rapid cycling, in which lithium is less effective), the second-generation antipsychotics more effectively decrease symptom severity and have a shorter time to remission. Thus patients with more severe symptoms are typically treated with a second-generation antipsychotic combined with either lithium or valproate.

Management of persistent or breakthrough manic/hypomanic episodes: Check medication adherence, as this is frequently a problem among patients with bipolar disorder. The serum levels of carbamazepine, divalproex, and lithium can be checked to verify medication adherence and/or absorption (Table 17-4). Next, the medication dose may be increased. Carbamazepine is frequently used when patients do not respond to first-line medications because it has similar efficacy to lithium and divalproex. Second-generation antipsychotics are also frequently prescribed when other first-line medications are not sufficient. If the patient is already on a second-generation antipsychotic, he or she may be switched to another.

Use of antidepressant medication: Antidepressant medications may trigger or exacerbate manic episodes in people with bipolar disorder. Antidepressant medications should therefore never be used to

Table 17-4. Commonly Used Mood Stabilizers: Adult Doses and Side Effects

MEDICATION	INITIAL DOSE (mg/day)	TARGET LEVEL	MAXIMUM DOSE (mg/day)	COMMON SIDE EFFECTS
Antimanic				
Lithium (Eskalith)	Immediate release: 900 (divided tid-qid) Controlled release: 900 (divided bid)	0.7-1.2 mEq/mL	Adjust to target level	Anorexia, nausea, vomiting, diarrhea, abdominal pain, excessive salivation, flatulence, indigestion, tremor, polyuria, polydipsia, weight gain, edema
Anticonvulsants				
Divalproex (Depakote)	750 (divided tid)	60-116 μg/mL	Adjust to target level	Nausea, somnolence, dizziness, ataxia, vomiting, asthenia, abdominal pain, dyspepsia, rash, alopecia, nervousness, tremor
Carbamazepine (Tegretol)	Regular: 200 bid Extended release: 200 bid	7-12 μg/mL	1600 (divided tid-qid) Extended release: 1600 (divided bid)	Dizziness, nausea, somnolence
Oxcarbazepine (Trileptal)	600 (divided bid)	NA	2100 (divided bid)	Fatigue, asthenia, nausea, vomiting, abdominal pain, diarrhea, dyspepsia, headache, dizziness, somnolence, ataxia, nystagmus, abnormal gait, diplopia, vertigo, vision abnormalities
Lamotrigine (Lamictal)	25 *50 †25 qod	NA	200 *400 (divided bid) †100	Back pain, fatigue, abdominal pain, nausea, constipation, vomiting, insomnia, somnolence, dry mouth, rhinitis, cough, pharyngitis, rash

(*Continued*)

Table 17-4. Commonly Used Mood Stabilizers: Adult Doses and Side Effects—cont'd

Second-Generation Antipsychotics				
Aripiprazole (Abilify)	10	NA	30	Headache, asthenia, accidental injury, nausea, dyspepsia, vomiting, constipation, agitation, anxiety, insomnia, somnolence, akathisia, lightheadedness, extrapyramidal syndrome
Olanzapine (Zyprexa)	Monotherapy: 15 Combination: 10	NA	Monotherapy: 30 Combination: 20	Accidental injury, asthenia, fever, back pain, dry mouth, constipation, dyspepsia, ecchymosis, weight gain, extremity pain, joint pain, somnolence, insomnia, dizziness, abnormal gait, rhinitis, cough
Quetiapine (Seroquel)	100 (divided bid)	NA	800 (divided bid)	Headache, pain, asthenia, tachycardia, dry mouth, constipation, vomiting, dyspepsia, weight gain, agitation, somnolence, dizziness
Risperidone (Risperdal)	2.5	NA	6	Dystonia, akathisia, dizziness, parkinsonism, somnolence, agitation, mania exacerbation, dyspepsia, nausea, increased salivation, generalized pain, myalgia, vision abnormalities

*If patient taking carbamazepine, phenytoin, phenobarbital, primidone, rifampin and not on valproate.
†If patient taking valproate.
NA, Not applicable.

treat bipolar disorder without a mood stabilizer, and may need to be discontinued during a manic episode. When patients switch from depression to mania or hypomania in response to an antidepressant, it should be discontinued and a mood stabilizer started instead.

Medication side effects: Lithium, divalproex, and carbamazepine exhibit similar rates of side effects (see Table 17-4). Lithium's side effects are typically dose related. The second-generation antipsychotics exhibit higher rates of side effects, particularly increased appetite, weight gain, and sedation.

Medication adverse effects: Most of the medications commonly used to treat bipolar disorder have been associated with significant adverse effects. Therefore, patients should be monitored periodically with laboratory testing and evaluations for the more common or serious adverse events characteristic for each medication (Table 17-5). Laboratory testing and evaluations should, at minimum, occur at baseline, after 3 months of therapy and periodically thereafter.

Table 17-5. Adverse Effects Associated with Mood Stabilizers, Recommended Evaluations

MEDICATION	ADVERSE EFFECTS	RECOMMENDED EVALUATIONS
Carbamazepine (Tegretol)	Hepatic enzyme elevation, aplastic anemia, agranulocytosis, thrombocytopenia, leukopenia, cortical lens opacities	Hepatic function indices, complete blood count, ophthalmologic examination
Divalproex (Depakote)	Hepatic failure and hepatotoxicity, hyperammonemia, thrombocytopenia, coagulopathy, pancreatitis	Hepatic function indices, ammonia (if indicated), complete blood count, prothrombin time, partial thromboplastin time and INR
Lithium (Eskalith)	Hypothyroidism, renal dysfunction, cardiac conduction delays	Thyroid-stimulating hormone, blood urea nitrogen, creatinine, electrocardiogram
Second-generation antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone)	Metabolic syndrome, extrapyramidal syndrome, hyperglycemia, hyperlipidemia, cortical lens opacities	Fasting serum glucose, fasting lipids, body weight, body mass index, waist circumference, ophthalmologic examination

INR, International normalized ratio.

Maintenance pharmacotherapy: Lithium, valproate, lamotrigine, olanzapine, and aripiprazole are proven to maintain remission. The benefits of maintenance therapy with second-generation antipsychotics should be balanced with the potential for side effects and adverse effects such as risk for metabolic syndrome.

Use of psychotherapy and psychosocial interventions: There is little evidence to support the use of psychotherapy to treat manic symptoms. However, during the maintenance phase of bipolar disorder, counseling should always be combined with pharmacotherapy. Ongoing psychotherapy and other psychosocial interventions may be helpful during maintenance therapy to address issues of treatment adherence, lifestyle adaptations, early recognition of bipolar symptoms, and interpersonal relationships. In particular, the following treatments have proven efficacy in preventing relapse: cognitive therapy, interpersonal social rhythm therapy, education about early recognition of bipolar symptoms, and psychoeducation for patients' families.

HYPOMANIC EPISODE

This is a distinct period of persistently elevated, expansive, or irritable mood that is different from the patient's usual nondepressed mood, with symptoms lasting at least 4 days. The episode leads to an unequivocal, observable change in functioning that is uncharacteristic of the person when he or she is not symptomatic. However, the disturbance is *not* severe and does *not* cause marked impairment in occupational, social, or interpersonal relationship functioning; requirement for hospitalization; or psychotic features. At least three of the previously noted persistent and significant manic symptoms are required (four if the mood is only irritable).

Signs

- Grandiosity
- Pressured speech
- Flight of ideas
- Easy distractibility
- Psychomotor agitation or retardation

MAJOR DEPRESSIVE EPISODE

Symptoms

- Depressed mood (children: may be irritable mood) +++++
- Anhedonia, diminished interest or pleasure in all or almost all activities +++++
- Weight gain (more common) or weight loss (change of more than 5% body weight within 1 month), or change in appetite (increase more common than decrease) (children: failure to achieve expected weight) +++

- Hypersomnia (most common manifestation), early morning awakening or insomnia ++++
- Fatigue, loss of energy or sense of being "slowed down" ++++
- Restlessness ++++
- Feelings of worthlessness or excessive or inappropriate guilt ++++
- Diminished ability to think, concentrate, or make decisions ++++
- Recurrent thoughts of death, suicidal ideation, or recent suicide attempt ++

Comments and Treatment Considerations

There is little evidence to guide decisions regarding medication and psychotherapeutic treatment for depressive episodes in bipolar disorder. Mood stabilizers are the primary treatment. Antidepressant medications may trigger or exacerbate manic episodes in people with bipolar disorder. Antidepressant medication should therefore never be used to treat bipolar disorder without one or more mood stabilizers.

Selecting an initial medication: The American Psychiatric Association (APA) recommends initiation of either lithium or lamotrigine. If monotherapy is ineffective, combinations of mood stabilizers are recommended. Typical combinations include lithium and lamotrigine; lithium and second-generation antipsychotics; mood stabilizers and SSRIs; and mood stabilizers and bupropion. Antidepressant medication should only be started in association with one or more mood stabilizers or second-generation antipsychotics. SSRIs or bupropion are preferred because they have lower rates of triggering an episode of mania or hypomania compared with other antidepressants. Lithium is less effective for bipolar II, mixed episodes, and rapid cycling. Any depressive episode with psychotic features should be treated with an antipsychotic.

Treatment for persistent or breakthrough depressive episodes: Check medication adherence, as this is frequently a problem among patients with bipolar disorder. Check the serum levels of carbamazepine, divalproex and lithium (see Table 17-4). Inquire about medication side effects (see Tables 17-2 and 17-4). If adherence is adequate and there are no significant side effects, consider increasing the medications toward their maximum daily dose or to the maximum doses the patient will tolerate. If symptoms remain partially remitted, consider adding another mood stabilizer or adding a second-generation antipsychotic. It is not unusual for a patient with bipolar disorder to require two or three mood stabilizers, or a second-generation antipsychotic. If the depressive symptoms are still inadequately treated, an antidepressant medication may be added.

Maintenance pharmacotherapy: See the manic episode section. Lithium and lamotrigine are proven to maintain depression remission. There are insufficient data to determine whether antidepressant medications should be considered in maintenance treatment.

Use of ECT: Typically ECT is reserved for patients exhibiting suicidal ideation, suicide attempts, psychosis, severe depression,

treatment-resistant depression, and depression with catatonic features. Periodic ECT may be continued as maintenance therapy if it was needed to achieve remission.

Use of psychotherapy and psychosocial interventions: See the manic episode section.

MIXED EPISODE

A mixed episode simultaneously meets criteria for both a manic episode and a major depressive episode (except for duration) every day for at least 1 week. The disturbance is severe, causing one of the following: marked impairment in occupational, social, or interpersonal relationship functioning; requirement for hospitalization to prevent harm to self or others; and psychotic features.

RAPID CYCLING

Rapid cycling is a DSM-IV specifier that can be applied to either bipolar I or bipolar II disorder. It is characterized by rapid alternation between separate mood disturbance episodes. Separate episodes are distinguished by either switches to an episode of opposite polarity (e.g., from a depressive to manic mood disturbance) or 2 months of full or partial remission between episodes. There are at least four separate episodes in a 12-month period.

DEPRESSION

Signs

- Flattened affect
- Tearfulness
- Poor eye contact
- Observable psychomotor agitation or retardation

GENERAL WORKUP FOR BIPOLAR DISORDERS

The clinical interview and mental status examination are used to make a diagnosis of a bipolar illness. Exclude the following before making these diagnoses:

- Manic or hypomanic episodes caused by antidepressant treatment (e.g., medication, ECT, light therapy)
- Other psychiatric illnesses, including schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, and psychotic disorder

- General medical conditions solely responsible for the symptoms (cerebrovascular accident or other CNS lesion, viral illnesses, hyperthyroidism, hypothyroidism, anemia, Cushing's disease, diabetes mellitus, malignancy, CAD, CHF, autoimmune disorders)
- Side effects of medications: steroids or substance abuse, intoxication, or withdrawal (e.g., from alcohol, cocaine, or amphetamines)

Comments and Treatment Considerations

There are two treatment phases: acute and maintenance. The acute phase starts at initial presentation and ends when bipolar symptoms have remitted. During this period treatment modalities are implemented and adjusted until the manic or depressive symptoms resolve. The maintenance phase, designed to prevent or delay recurrence of manic/hypomanic or depressive episodes, involves continued long-term treatment at the effective acute phase dose. Sometimes adjunctive medications can be discontinued in the maintenance phase. However, all patients with bipolar disorder require some form of long-term maintenance treatment. Treatment guidelines have been published by several organizations including the APA and the Canadian Network for Mood and Anxiety Treatments (CANMAT).

Patients with bipolar disorder require pharmacotherapeutic interventions. In fact, most patients require two or more medications to control their symptoms. Psychotherapeutic interventions alone are not proven effective for manic episodes or depressive episodes associated with bipolar disorder. Commonly used medications are listed in Table 17-4.

The treatment modalities in Table 17-5 can be used in bipolar I, bipolar II, and cyclothymia.

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